

## REMARKS

The claims, as amended in the current Response, are directed to a pharmaceutical composition comprising particles comprising a polymeric material, a biologically active agent capable of generating a protective immune response in an animal or a human, a cationic pluronic and N-carboxymethyl chitosan or a salt thereof. Prior to the current Response, Claims 1, 5, 6, 11-17, 20-22, 37 and 44-71 were pending. Applicants cancel Claims 1, 5, 6, 11-17, 20-22, 37, 44-51, 57, 64-65 and 67 and amend Claims 52-56, 58, 61-63, 66, 68 and 71. The amendments do not add any new matter and are supported throughout the application, as filed, for example, on page 11, lines 6-24, page 13, lines 8-15, and page 21, lines 4-5 and 25-29, of the specification. Claims 52-56, 58-63, 66, and 68-71 will be pending after entry of the current Response.

### Rejection under 35 U.S.C. §102(a)

*Amsden et al. (WO 99/57176; "Amsden")*

The Examiner rejects Claims 1, 5-6, 11-15, 20, 44-48, 51, 62, 65-68 and 71 under 35 U.S.C. §102(b) as anticipated by Amsden. Applicants cancel Claims 1, 5-6, 11-15, 20, 44-48, 51, 65 and 67, thereby rendering their rejection moot. Applicants respectfully assert that the amendments to independent Claim 62 overcome the rejection of Claim 62 and its dependent Claims 66, 68 and 71.

Claims 62, 66, 68 and 71, as submitted in the current Response, recite particles comprising "a cationic pluronic," among other components. Applicants previously discussed Amsden in the Amendment and Response to Final Office Action filed February 13, 2009 ("previous Response"). Applicants further assert that Amsden fails to teach or suggest particles comprising a cationic pluronic and therefore fails to teach each and every element of the claim, as required for anticipation in MPEP 2131. Applicants respectfully assert that Amsden fails to anticipate Claims 62, 66, 68 and 71 for at least this reason and request withdrawal of the rejection.

### Rejections under 35 U.S.C. §103(a)

MPEP 2142 states: "To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill

in the art' when the invention was unknown and just before it was made. In view of all the factual information, the examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at that time to that person." To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquiries, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and (c) resolving the level of ordinary skill in the pertinent art. See MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

*Eyles (Vaccine Vol. 16(7):698-707 (1998); "Eyles") in view of Amsden*

The Examiner rejects Claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62 and 65-71 under 35 U.S.C. §103(a) as obvious over Eyles in view of Amsden. Applicants cancel Claims 1, 5-6, 11-17, 20-22, 37, 44-51, 65 and 67, thereby rendering their rejection moot. Applicants respectfully assert that the amendments to independent Claim 62 overcome the rejection of Claim 62 and its dependent Claims 66 and 68-71.

As discussed in the previous sections of the current Response, the rejected claims, as currently amended, recite particles comprising a cationic pluronic, among other components. Applicants discussed the scope and content of Eyles and Amsden in the previous Response. In addition, applicants bring to the Examiner's attention that Amsden teaches a method for the manufacture of microspheres, but fails to teach or suggest using cationic pluronic as a component of the microspheres. See, for example, Amsden, page 4, lines 14-18. Eyles teaches compositions of plague vaccine encapsulated in poly (L-lactide) microspheres, but fails to teach or suggest adding a cationic pluronic to the particles to improve their immunogenic properties. For at least this reason, a combination of Amsden and Eyles does not disclose or suggest all elements of the particles recited in Claims 66 and 68-71. At least in view of these differences between the cited combination and the claimed embodiments of applicants' compositions, the claims would not have been obvious to one of ordinary skill in the art in the field of the present application at its priority date.

Furthermore, applicants discovered that addition of a cationic pluronic to the particles recited in the pending claims leads to an unexpected and advantageous result, improved immunogenicity of the particles. Applicants disclose, for example, in Example 16, on pages 21-

22 of the specification, and in Figure 6 of the present application that cationic pluronic enhances immunogenic properties of particles comprising a chitosan and an antigen. In view of this unexpected advantage and the differences between the claims and the disclosure provided in the combination of Eyles and Amsden, applicants respectfully request withdrawal of the rejection.

*Illum (WO 97/20576; "Illum") in view of Amsden*

The Examiner rejects Claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62 and 65-71 under 35 U.S.C. §103(a) as obvious over Illum in view of Amsden. Applicants cancel Claims 1, 5-6, 11-17, 20-22, 37, 44-51, 65 and 67, thereby rendering their rejection moot. Applicants respectfully assert that the amendments to independent Claim 62 overcome the rejection of Claim 62 and its dependent Claims 66 and 68-71.

As discussed in the previous section, the rejected claims, as currently amended, recite particles comprising a cationic pluronic, among other components. Applicants discussed the scope and content of Illum and Amsden in the previous Response. The scope and content of Amsden is further discussed in the previous sections of the current Response. Applicants further note that Illum teaches the use of chitosans as adjuvants in vaccine compositions, but fails to address the use of N-carboxymethyl chitosan in the compositions comprising particles. Thus, a combination of Illum and Amsden does not disclose or suggest all elements of the particles recited in Claims 66 and 68-71. The combination of Illum and Amsden also fails to teach or suggest the use of cationic pluronic to improve immunogenicity of the particles, which is an unexpected and advantageous result that applicants discovered. At last in view of this unexpected advantage and the above differences between the claims and the disclosure provided in the combination of Illum and Amsden, applicants respectfully request withdrawal of the rejection.

*Duncan et al. (WO 94/20070; "Duncan") in view of Amsden*

The Examiner rejects Claims 1, 5-6, 11-15 and 20-22 under 35 U.S.C. §103(a) as obvious over Duncan in view of Amsden. Applicants respectfully assert that cancellation of these claims renders their rejection moot.

Applicants further assert that a combination of Duncan and Amsden fails to render obvious the pending claims, which recite particles comprising a cationic pluronic, among other components. The scope and content of Amsden is discussed in the previous Response and elsewhere in the current Response. Applicants also discussed the scope and content of Duncan in the previous Response. Applicants further note that Duncan discloses on page 9 the use of Pluronic® block copolymers, in particular, of L-121, as surface-active agents in adjuvant emulsions including squalene, along with other components. According to Duncan, Pluronic® block copolymers “are used to make stable squalene emulsions.” However, Duncan fails to teach or suggest the use of cationic pluronics in particles in order to improve their immunogenicity, an unexpected and advantageous result that applicants discovered.

Furthermore, a combination of Duncan and Amsden fails to disclose or suggest all elements that would result in particles coated or surface-modified with N-carboxymethyl chitosan or a salt thereof (Claim 53), particles, wherein N-carboxymethyl chitosan or a salt thereof is adsorbed onto a surface of the particles (Claim 54), or particles coated with N-carboxymethyl chitosan or a salt thereof and a biologically active agent adsorbed onto the coated particles (Claim 63). In view of the unexpected advantages of the claimed embodiments of applicants’ invention, discussed above, and in view of the differences between the claims and the disclosure provided in the combination of Duncan and Amsden, applicants respectfully assert that the currently pending claims are allowable in view of the cited combination.

*Illum or Eyles and Amsden, further in view of Clearly et al. (WO 96/21432; “Clearly”)*

The Examiner rejects Claims 52-61, 63 and 64 under 35 U.S.C. §103(a) as obvious over Illum or Eyles, Amsden, as applied to Claim 62 in the previous sections of the Office Action, and further in view of Clearly. Applicants cancel Claims 57 and 64, thereby rendering their rejection moot. Applicants respectfully assert that the combination of the publications cited by the Examiner fails to render obvious independent Claims 52 and 63, as well as Claims 53-56 and 58-61, dependent on Claim 52.

The scope and content of Illum, Eyles and Amsden is discussed in the previous Response and elsewhere in current Response. Clearly disclosed particles comprising an active substance and a mucoadhesive polymer. According to Clearly, the mucoadhesive particles can

be produced by uniformly mixing an active substance with a mucoadhesive polymer or by coating the active substance core with a layer of the mucoadhesive polymer. The list of suitable mucoadhesive polymers disclosed in Clearly on page 7. *See*, for example, Clearly, page 6, line 26, through page 7, line 28. Clearly does not teach or suggest using N-carboxymethyl chitosan as a mucoadhesive polymer.

The Examiner states that it would have been obvious to modify the particles disclosed in Eyles or Amsden with N-carboxymethyl chitosan at the surface of the particles, as taught in Clearly, in order to arrive at the claims. Applicants respectfully disagree. Applicants bring to the Examiner's attention that the list of suitable mucoadhesive polymers disclosed in Clearly on page 7, overlaps, for example, with the list of polymers disclosed on page 9 in Amsden. Thus, one would be able to produce the particles, as proposed in Clearly, using at least some of the polymers disclosed in Amsden and without any further surface modification with N-carboxymethyl chitosan proposed by the Examiner. It is therefore not clear why the disclosure of Clearly would have made it obvious to proceed with a N-carboxymethyl chitosan modification of the particles disclosed in Amsden, and why such a modification would have been reasonably expected to succeed in improving delivery and release of active agents at the mucosal surfaces, as the Examiner suggests on page 18 of the Office Action.

The disclosure of Clearly suggests that using certain polymers, either uniformly throughout the particles or as an outside layer, would improve mucoadhesive properties of the particles. *See*, for example, the paragraph bridging pages 6 and 7 of Clearly. Clearly provides a list of suitable mucoadhesive polymers on page 7, and N-carboxymethyl chitosan is not included in the list. Applicants assert that, based on the disclosure of Clearly, one of ordinary skill in the art in the are of the present application would think that using one of the listed polymers would be enough to result in mucoadhesive particles. Clearly fails to suggest that adding N-carboxymethyl chitosan to the particles that already include a mucoadhesive polymer, such as carboxymethylcellulose, listed both on page 7 of Clearly and on page 9, line 24, of Amsden, would result in any further improvement of the particles' properties. To the contrary, the disclosure of Clearly suggests to one of ordinary skill in the art that incorporating a mucoadhesive polymer, for example, carboxymethylcellulose, into the particles is enough to

render the particles mucoadhesive. The disclosure of Clearly therefore teaches away from further modification with N-carboxymethyl chitosan.

Accordingly, a combination of Clearly and Amsden fails to suggest a modification with N-carboxymethyl chitosan proposed by the Examiner. Illum fails to teach or suggest the use of N-carboxymethyl chitosan in particles, and therefore does not add any knowledge relevant to one of ordinary skill in the art in the area of the present application to the disclosure of Amsden and Clearly. Contrary to the Examiner's statement on page 18 of the Office Action, and as discussed in the previous Response, Eyles fails to teach or suggest adding N-carboxymethyl chitosan to improve the properties of the encapsulated plague vaccine that it discloses. At least for the foregoing reasons, applicants assert that the modification proposed by the Examiner on page 18 of the Office Action would not have been obvious to one of ordinary skill in the art in the field of the present application, at its priority date.

Furthermore, the rejected claims, as currently amended, recite particles comprising a cationic pluronic, among other components. Cationic pluronic improves immunogenic properties of the particles, an unexpected and advantageous result that applicants discovered. In addition, the combination of the publications cited by the Examiner in this section of the Office Action fails to disclose or suggest all elements that would result in particles coated with N-carboxymethyl chitosan or a salt thereof and a biologically active agent adsorbed onto the coated particles, as recited in Claim 63. In view of this unexpected advantage and the differences between the claims and the disclosure provided in the combination of the publications cited by the Examiner, applicants respectfully request withdrawal of the rejection.

### **Claim Objections**

The Examiner objects to Claims 44, 52 and 62, due to the recitation of the term "first material." The Examiner objects to Claims 63-64 due to the recitation of "at least a part of the immunostimulating amount of N-carboxymethyl chitosan." Applicants cancel Claims 44 and 64, thereby rendering their rejection moot. Applicants assert that the claim amendments, which delete the objectionable terms, overcome the objections to Claims 52, 62 and 63. Applicants request withdrawal of the objections.

## **CONCLUSION**

This Response fully addresses the rejections in the Final Office Action mailed April 30, 2009. Based upon the amendments and remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by an Examiner's Amendment, or that there are any other issues that can be resolved by a telephone interview, a telephone call to the undersigned attorney at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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